RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GEORGE H. YOO

Appeal 2007-2864
Application 10/747,798
Technology Center 1600

Oral Hearing Held: Wednesday, September 12, 2007

Before ERIC GRIMES, LORA M. GREEN, and
RICHARD M. LEBOVITZ, Administrative Patent Judges

ON BEHALF OF THE APPELLANTS:

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The above-entitled matter came on for hearing on Wednesday, September 12, 2007, commencing at 1:45 p.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, 9th Floor, Hearing Room A, Alexandria, Virginia, before Jan M. Jablonsky, Notary Public.

JUDGE GRIMES: Good afternoon, Ms. De La Paz.

As you may know, you'll have 20 minutes to present your arguments, and we do have a lot of cases this afternoon, so we're going to have to stick pretty closely to that 20 minutes. Start whenever you're ready.

MS. DE LA PAZ: Good afternoon, Your Honors.

The subject matter of the present invention that's under consideration today pertains to methods of inhibiting the growth of a papillomavirus. The methods involve topically applying to lesions that include papillomavirus infected cell, a composition that includes an expression cassette that includes a promoter, operably coupled to a gene-encoding p53.

Now, there are rejections of two types that are involved in this appeal. First, there are four rejections under Section 102 and two rejections under Section 103. The main issue in this appeal is whether the claims are inherently anticipated by any of the Clayman references, the recombinant advisory committee meeting minutes or the Nielsen reference. Taking these one-by-one, the Clayman reference is a research protocol of Clayman which describes a proposal to administer by intramucosal injection a composition that includes Adenovirus Ad-p53 into the lesions, followed by swishing of the lesions in the mouth.

The Recombinant Advisory Committee meeting minutes, which I'll just abbreviate -- the RAC meeting minutes is meeting minutes from the

Committee of the National Institutes of Health in Clayman describing his own particular invention pertaining to that was set forth in the Clayman reference, namely intramucosal injection of ADP53 followed by oral swishes. Nielsen is a published PCT application which describes combination p-53 plus gemcitabine to treat cervical and head and neck cancers. None of these references, either Clayman, the RAC meeting minutes, or Nielsen expressly set forth any information regarding any papillomavirus infection of any cell in any lesion.

Now, the Examiner pulls in two additional references to make his case for inherent anticipation. The Oda reference is a study which describes in its background section a study wherein, in a sample of patients with oral carcinoma, up to 90 percent had HPV DNA in the lesions. The Flaitz reference, which he also cites as supporting inherent anticipation, cites to a study of oral pre-malignancies for up to 42 percent of the lesions had HPV-infected DNA.

So, basically, the Examiner concludes that there must be inherent anticipation because Oda inflates teach that in some patients there's HPV infection. However, the Examiner applies an incorrect standard for determining an inherent anticipation. I direct you to a Federal Circuit case from 1991, Continental Can Company v. Monsanto. And I quote: "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence that such evidence must make clear that the missing descriptive subject matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill in the art. Here, the Examiner has not shown that any of the lesions that would

have been treated in Clayman, the RAC minutes, or Nielsen necessarily included HPV-infected cells.

JUDGE GREEN: I'm sorry.

JUDGE GRIMES: Go ahead.

JUDGE GREEN: Don't Oda and Flaitz show that if you treat 100 patients, one of ordinary skill in the art would have expected at least 42 to have HPV? So, what you're saying, to me -- it seems to me that you're arguing unless Oda and Flaitz, say, HPV is involved in 100 percent of these lesions, you can't have any anticipation.

MS. DE LA PAZ: Well, another study we cited in the background section of the specification is Gilson, and that was made of record in the IDS that C39. In that study, they looked at a sample of patients of newly diagnosed carcinoma and found 25 percent of patients had papilloma-positive DNA. So, how much is too much?

JUDGE GREEN: But even if he has 25 out of 100, at least in that 25, I mean, HPV is known to be involved in these types of lesions. And that seems to me something that the Examiner established is well-known in this particular art.

MS. DE LA PAZ: Well, he may have established there may be some association, but let's look again. Here's another case from the Fed Circuit -- Mehl/Biophile v. Milgraum. That's a Federal Circuit case from 1999. In that case, the claims recited directing a laser in a vertical direction towards a hair follicle. In the prior art that was cited as inherently anticipating the reference involved directing a laser at tattoo pigment on a skin lesion. And the argument was, well, there's inherent anticipation, because one could have vertically aligned the laser with a hair follicle that

might have been in the region of the tattoo pigment. And the Federal Circuit said no, the mere possibility that such an alignment does not legally suffice to show anticipation and that occasional results are not inherent. So, occasional results are not inherent.

JUDGE GREEN: This is a different case because you don't have a possibility that even using your number, 25 percent, if you treat 100 patients, you have a probability, not a possibility that 25 of those 100 patients are going to have the HPV involvement.

MS. DE LA PAZ: Well, a possibility is a possibility. It's very possible that none of those patients could have HPV involvement in any of those studies.

JUDGE LEBOVITZ: Clayton actually looked at the HPV status of the patient, and doesn't that establish that he knew that a certain fraction of those patients were going to be HPV-positive?

MS. DE LA PAZ: Well, he looked at a fraction of patients, but again, the standard for inherent anticipation is whether the limitation is necessarily present. They may not be present.

JUDGE LEBOVITZ: What about Perricone ,where they were putting vitamin C on the face to protect against sunburn? Not all people who put it on were going to go out and get into the sun, but the fact is the population was susceptible to sunburn. So, in the same way, you know that the population of people that are being treated by Clayman, a certain percent will actually have the HPV-positive.

MS. DE LA PAZ: Well, I disagree. The fact is, you don't know that the population that will be treated by Clayman will definitely have HPV-infected cells. It's possible they may not.

JUDGE GREEN: So you want 100 percent certainty?

MS. DE LA PAZ: Well, a range in these studies from 25 percent to 42 percent to 90 percent shows at least that there's a lot of variability among those studies, and it's not unreasonable to B

JUDGE GREEN: But even if we take the lowest range, 25 percent, there is a correlation marked that HPV is involved in these types of malignancies or these types of lesions. I'm just asking you, the only way that you would say that we could have inherency is if say it was involved 100 percent?

MS. DE LA PAZ: The standard that the Federal Circuit has set forth is necessarily present. You know, yes, while there may be some recognition by persons of ordinary skill in the art, the standard also requires that the missing descriptive limitation necessarily be present.

JUDGE LEBOVITZ: But isn't it necessarily present in that population? And didn't the Examiner satisfy his burden? Because he can't go out and get the data from Claimant and actually know whether, in fact -- I don't remember what numbers were being treated, or in the other references -- but isn't it enough that he's saying we know that 25, 90 percent of the population have it -- have HPV -- so therefore that's enough to sustain the Examiner's burden -- because the Patent Office doesn't have the facilities to go out and actually do the comparisons themselves. So from a burden standpoint, why isn't that enough?

MS. DE LA PAZ: Well, again, Clayman and the RAC meeting minutes were protocols. You know, they didn't describe actual data. Nevertheless -- regardless of that -- it's not enough, because inherent requires necessarily present. Otherwise, you would be trying to figure out,

well, where do you cut the line? Is it 5 percent Is it 50 percent Is it 80 percent?

JUDGE GRIMES: Well, I think the line is one patient, right? If we knew that one patient had been treated as recited in this claim, we'd have a definite anticipation. Correct?

MS. DE LA PAZ: That's right. But we don't know. And that's the issue.

JUDGE GRIMES: But we know that the population is susceptible, and how could the Examiner ever make a case if he actually -- hasn't the Examiner satisfied his burden by showing you that there's a factual probability?

MS. DE LA PAZ: No. He has not satisfied his burden. Out of the Mehl/ Biophile v. Milgraum case cited to In re Oelrich, which states that "inherency may not be established by probabilities or possibilities, and that occasional results are not inherent." So, that being said, appellants respectfully request that the Board reverse the rejections under 102 pertaining to the RAC meeting minutes, Clayman, and Nielsen.

Now, just as far as a couple of dependent claims briefly, dependent claim 4 is additionally not anticipated by any of those rejections because dependent claim 4 recites, "wherein, the cell is a keratinocyte, and a keratinocyte is a cell that makes keratin. Oral mucosa and cervical mucosa are not lined by keratinocytes. The Examiner cites Flaitz as teaching that keratinocytes are squamous cells. While that may be true, it doesn't teach that Clayman, the RAC meeting minutes or Nielsen included keratinocytes. The oral cavity is not lined by keratinocytes.

Now, as to claim 6, which recites, "wherein the cell is a skin cell," the Examiner argues that that claim is anticipated because he broadly argues that skin includes the lining of certain body cavities like the cervix and the mouth. However, the ordinary and customary meaning of terms, as you know, are evidenced by a variety of sources including the written description and claims and contrary to the Examiner's assertion, the ordinary and customary meaning of the term "skin" does not include mucosal tissues like the mouth or the cervix. As evidence, we cite to originally filed claim 6, which recites, "wherein the cell is a skin cell," and originally-filed claim 7, which recites, "wherein the cell is a mucosal cell." The fact that both claims depend from claim 1 supports the ordinary meaning, whereby, skin is distinct from mucosa.

JUDGE GRIMES: Why are those inconsistent with the Examiner's definition? They could just be dependent claims of different scope.

MS. DE LA PAZ: The Examiner argues that the claims are anticipated because the mouth is lined by skin, and we disagree. We argue for an ordinary and customary interpretation of skin that is distinct from mucosa of the mouth.

JUDGE GRIMES: I understand that. I'm just asking, do you have another basis for making that distinction, because I'm not really seeing that this necessarily supports your position.

MS. DE LA PAZ: Well, in our reply brief we cited to numerous places in the specification where we separately discuss skin versus mucosa, keratinocytes versus mucosa versus skin, and all those things

support an ordinary interpretation such that skin does not encompass mucosa of the oral cavity or the lining of the cervix. If you'd like, I can go over this.

JUDGE GRIMES: I can look at it. If it's in the reply brief, I can find it.

MS. DE LA PAZ: So there's one additional rejection under 102, which is not an inherent anticipation issue. The Examiner cites the El-Deiry reference as anticipating the claims. Now, El-Deiry discusses treatment of lesions that include papillomavirus-infected cells with a topical gene therapy using a viral vector that expresses p73, which is a different molecule than p53.

JUDGE GREEN: But El-Deiry specifically calls p73 a homolog of p53, correct?

MS. DE LA PAZ: El-Deiry does refer to P73 as a homolog of p-53. In our specification, we recite at page 14, lines 5 through 6, "throughout this application the term p-53 is intended to refer to the exemplified p53 molecules as well as all p-53 homologs from other species. So, stepping back, what do we mean by the exemplified p-53 molecules?

Well, one of ordinary skill in the art would have understood that from the specification that this is human p53. He or she would understand this to be the case because the section of the application where this definition appears addresses in detail the role of p53 in human cancer. And that's on pages 12 through 14 of the specification.

Indeed, the application is replete with reference to p-53, its role in human cancer and the role of human papillomavirus in human cancer. So, one of ordinary skill in the art would understand that if the exemplified p53 molecule was a human p53, then in the context of the present specification,

the phrase, "all p53 homologs from other species refers to p53 molecules that are from non-humans, such as, for example, rat p53, mouse p53, dog p53, et cetera.

El-Deiry contains no disclosure pertaining to administration of any p53 molecules to any papillomavirus-transformed cell. Nor does it disclose any p53 molecule from another species. And we've set forth in a declaration from Dr. Louis Zumstein evidence to support an understanding that p53 in the present specification does not include p73, and that's Exhibit 8 of the appeal brief.

Dr. Zumstein is a person of skill in the art with over 13 years of experience in the biotechnology field, and he has read through the specification, and it has declared that it is his belief that p73 is not homolog of p53.

JUDGE GRIMES: What is p73?

MS. DE LA PAZ: P73 is a molecule that is structurally different. It has some sequent similarities to human p53, but many sequence dissimilarities. It's not involved in carcinogenesis, per se. It's not involved in self-cycle growth.

If you look at our application, one of the areas of interest as to p53 was the fact that the E6 protein that's made by papillomavirus binds to p53 and causes degradation of p53. So our invention sought to administer p53 to correct that deficiency.

JUDGE GRIMES: But p73 presumably does not bind to E6.

MS. DE LA PAZ: P73 does not bind to E6. No. It does not. It does not undergo degradation.

JUDGE GRIMES: What does it do?

MS. DE LA PAZ: Pardon?

JUDGE GRIMES: What does it do?

MS. DE LA PAZ: I don't know, specifically. But anyway, all these things support our argument that p53 as set forth in our application does not include p73 of El-Deiry.

Now, the Examiner has cited to Kaghad as supporting his assertion that El-Deiry anticipates the claimed invention. Kaghad describes the sequence of p73, and again, while there might be some sequence similarity of p73 to p53, it makes clear in Kaghad that there are substantial sequence to similarities as well. Further, Kaghad specifically notes that "it is not obvious that p73 and p53 share common functions." This further supports appellants' position that p73 is not a homolog of p53 in the context of the present specification.

Further, regarding dependent claims, El-Deiry additionally does not anticipate claims 4, 6 or 6, because it does not disclose treatment of any keratinocyte or treatment of any skin cell.

Therefore, appellants respectfully request reversal of the rejection under 102 based on El-Deiry.

The last issue in this case pertains to a rejection under 103. The Examiner has argued that a subset of the claims are rendered obvious by the RAC meeting minutes in view of Oda and Flaitz, or El-Deiry in view of Zhang. Now, the Examiner has not met the Patent Office's burden of establishing a prima facie case of obviousness, because he has not shown that the cited combination of references provide any reasonable expectation of success to inhibit the proliferation of papillomavirus-infected cells.

Now, going back to the RAC meeting minutes, that was the minutes of a NIH committee meeting to discuss the Clayman protocol to administer intramucosal at p53 followed by oral swishes. Again, there's nothing in that reference that specifically sets forth any inhibition of the growth of a papillomavirus-infected cell. Oda and Flaitz, while they do make reference in their background sections to HPV-transformed cells, they don't provide any specific teaching or suggestion pertaining to gene therapy of papillomavirus-infected cells.

Oda actually is a reference that concerns chromosomal and cell-cycle changes in HPV-infected cells when grown and cultured. It does not even pertain to any in vivo studies or gene therapy. And Flaitz is a review article that concerns a discussion of virus infection and malignancies, and not gene therapy.

Further, as far as the El-Deiry reference just discussed, the fact that El-Deiry does not disclose p53 as the term p53 is discussed in the context of the present invention. It pertains to methods involving p73. Now, he combined Zhang with El-Deiry, but Zhang is only cited as teaching a flavorin, which is one of the limitations of some of the claims at issue.

Therefore, the Examiner hasn't established any reasonable expectation of success whatsoever that a person of ordinary skill when presented with the RAC meeting minutes and Oda and Flaitz, or El-Deiry and Zhang, would practice the claimed invention. Also, there's no prima facie case of obviousness, because there's suggestion or motivation to provide for the claimed invention based on these references. So he cites the Recombinant Advisory Committee meeting and El-Deiry as describing a

liquid delivery comprising an adenoviral vector to the mouth, and Zhang is teaching a flavorin.

However, the claims at issue are directed to inhibiting, suppressing, or preventing the growth of papillomavirus-transformed cells in a hyperplastic lesion, there's no specific motivation to provide for inhibiting, suppressing, or preventing the growth of a papillomavirus-transformed cell in a hyperplastic lesion using a flavorin composition that contains p53 in any of the references.

Quoting from In re Mills, a Federal Circuit case from 1990: "The mere fact that references can be combined or modified does not render the result and combination obvious unless the prior art also suggests the desirability of the combination. KSR also specifies that any analysis to argue that a suggestion in motivation must be made explicit, and here no such explicit analysis has been set forth.

So, in conclusion, in light of the above, none of the pending claims are properly rejected. Therefore, appellants respectfully request that the Board reverse the pending grounds for rejection.

JUDGE GRIMES: Any more questions?

JUDGE GREEN: No.

JUDGE GRIMES: Thank you, very much.

(Whereupon, at 2:06 p.m., the hearing was concluded.)